CDRH's Research on Biological Response to Metal-Containing Devices

The Center for Devices and Radiological Health (CDRH) recognizes that several significant scientific gaps exist in our understanding of host response to an implanted metal device including:

- Potential clinically meaningful adverse responses in patients
- Specific factors which may contribute to the identification of at-risk patient subpopulations
- Tests or methods to better predict or identify exaggerated immune responses i patients

Accordingly, CDRH has initiated research efforts, including working with external collaborators, to address the knowledge gaps in these areas as we also consider whether additional action may be appropriate to further promote device safety.

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Scientific Understanding of Immune Responses to Metal in Medical Devices

CDRH conducted an extensive review of the biological response to metal implants, which was published in September 2019. This paper presents CDRH's review of the available scientific information, including research articles and post-market surveillance data, related to metals and their use in medical implants. CDRH held a public advisory committee meeting of the Immunology Devices Panel in November 2019, which provided a platform for CDRH to present its findings and solicit feedback from the public and experts in the field. Based on our evaluation, CDRH identified several gaps in the current understanding of immunological response to metals in devices that should be addressed. Although limited, the current evidence suggests some individuals may develop a heightened local or systemic immune or inflammatory reaction when exposed to certain metals contained in select implantable devices.

The science of the immune response to materials in medical devices is evolving. To gain better understanding of how patients respond to materials used in medical device implants and to harness that information to improve the safety of devices in patients, CDRH is working to engage the public—in particular, scientists, patients, and health care providers—and industry stakeholders to determine the current state of the science, critical gaps in existing science, and what approaches CDRH and the medical device community should consider.

Research Areas

CDRH is undertaking research in several areas to further our knowledge and understanding of host responses to metal implants. CDRH anticipates that these and subsequent research efforts will form the foundation to develop the tools needed to improve premarket device evaluation of metal containing implants, the ability to screen and monitor patients, and the design of safer metal implants – all o which will help patients and physicians make informed benefit-risk decisions regarding their use. This research may also help expand our knowledge of host responses to other materials.

Scope and Occurrence of Metal Implant Related Adverse Health Outcomes

Issue: While a broad number of adverse events have been reported to be associate with metallic implants, the true scope and occurrence of these events that derive from patient exposure to specific metal alloys and certain device characteristics are not yet well established.

Scope of the Research: CDRH intends to clarify the frequency and device/material significance of adverse clinical outcomes that may be associated with metallic implants, by leveraging real world clinical data to identify correlations between patient/device characteristics and clinically manifested sequalae. This effort is intended to clarify the significance of device and/or metal alloy characteristics and patient characteristics regarding the potential for adverse outcomes, as well as curate the terminology and ontology of metal implant-related adverse outcomes. The hope is this effort will also provide insight into biological mechanisms that may underlie adverse health outcomes and contribute further to efforts in biomarker discovery and nonclinical test development for more predictiv evaluation of device performance in patient subgroups (see Biomarkers and Other Tools for Screening and Monitoring Patients).

Clinically Relevant In Vitro Tests and Safety Limits for Corrosion/Wear

Issue: While there are standardized in vitro test methods to assess the susceptibility of metallic devices to wear and corrosion, the implications of these te results for in vivo device performance, patient exposure, and ultimately risk, are no yet well established.

Scope of the Research: CDRH intends to engage in research efforts to better define the environment surrounding implants in different anatomical locations and use this information to develop more clinically relevant in vitro test methods and safety limits for the release of corrosion and wear debris from metallic devices. Evaluating medical devices under clinically relevant test conditions would enable better evaluation of the risks of corrosion and release of wear debris from metallic devices. Improved, clinically relevant safety limits will assist manufacturers in identifying test results which may imply safety concerns associated with a specific metallic device.

Impact of Anatomical Location and Device Characteristics on Immune Responses

Issue: While it is recognized that the location of an implanted device can impact immune responses, the relation between the device characteristics, including metal alloy, and the surrounding tissue have not been well established.

Scope of the Research: CDRH intends to work to elucidate the impact of contacting tissue and device/material characteristics on both innate and adaptive immune responses by using suitable animal and alternative models to study possibl effects of some medical devices, each with different principles of operation, materials of construction, and anatomical location of device use[1]. The results of these studies are intended to provide insight into tissue-specific adverse reactions post implantation including the variability of the immune response in different anatomical locations. We are hopeful the results can also assist in providing additional considerations in the development of nonclinical test methods to improv the predictability for tissue-specific adverse immune reactions post implantation in patients.

Clinically Relevant In Vivo and In Vitro Models for Immune Responses

Issue: The disease pathobiology resulting from metal implants largely includes immunogenic responses mediated through either hypersensitivity or other immune reactivity mechanisms. However, our current testing methods for metal allergies have been limited in capturing different biological, cellular, and molecular interactions between these 'foreign' devices and human tissues.

Scope of the Research: CDRH intends to develop in vivo and in vitro models th are predictive of device related immunogenic responses in patients. To meet this goal, we plan to use relevant in vivo models to assess systemic and localized responses and develop in vitro models (e.g. microfluidic systems and 2-D and 3-D cell/tissue culture systems. These models are intended to assess immune cell populations and their response in relation to implanted devices and released metal ions or metal particles. Once developed, these models could be integrated into a portfolio of nonclinical biocompatibility assessment assays and protocols to improv our ability to predict the potential for metallic devices to cause immunogenic responses in patients.

Standardized Sampling and Analysis of Corrosion/Wear Products in Biological Tissue/Fluids

Issue: Despite the availability of recognized consensus standards for the recovery and assessment of implanted medical devices and associated tissue/fluid specimen there is a large degree of variation and lack of consensus on best practices for sample collection and processing. In addition, while current consensus standards are focused on minimizing damage during sample recovery and gathering data at the proper time under appropriate circumstances, they are not geared toward developing clinically relevant standardized methods and acceptance criteria to evaluate periprosthetic tissue environments or the release of corrosion and wear debris from medical devices.

Scope of the Research: CDRH intends to identify the existing gaps in current consensus standards for the assessment of corrosion and wear debris and the associated biological responses in patients, as well as assess the consistency with which the methods relevant to sampling, histological examination, and physical, chemical and other analyses are applied. This research is intended to help identify steps needed to improve existing device-related consensus standards, potentially develop new consensus standards, and increase consistency in the sampling and subsequent analyses, thereby addressing current gaps in the predictability of device related nonclinical testing.

Optimization of Existing In Vitro Diagnostic Tests

Issue: Several diagnostic tests are presently available for some measure of metal sensitivity assessment for patients with metal implants including those aimed at assessing implant stability in vivo (exemplified by measurement of the concentration of metal ions in circulation), and the assessment of patient immune and inflammatory responses. This second category is constrained by knowledge gaj in the fundamental immunobiology of the host response to metal implants, the pathways involved, and particularly the identification of factors which may translat into poorer outcomes for metal-containing implants in contrast to well-tolerated, stable, functioning implants.

Scope of the Research: CDRH intends to identify and prioritize existing tests for improvements to analytical and clinical parameters. It will also look to refine and encourage harmonization of the regulatory landscape surrounding metal implant-related testing to aid development of novel biomarkers and methods that are clinically relevant to implant outcomes.

Biomarkers and Other Tools for Screening and Monitoring Patients

Issue: There is a lack of study endpoints and other metrics (including biomarkers as surrogate endpoints) that can enable predictive evaluation of real-world performance of metal implants. Existing tests such as metal ion levels in serum/blood are not sufficiently predictive of different adverse outcomes and other tests such as skin patch testing or lymphocyte transformation testing (LTT) are limited to identification of adaptive immune responses and allergic manifestations.

Scope of the Research: The CDRH's research efforts are intended to:

- Identify biomarker candidates using pre-existing epidemiological/clinical and genetic/genomic data,
- Corroborate the plausibility of the candidate biomarkers using in silico approaches[2], and
- Select the most promising candidates for future validation and development o non-invasive clinical tests for predicting and/or monitoring metal implant related adverse outcomes.

The resultant validated biomarkers could serve to facilitate development of non-invasive diagnostic/prognostic tests for pre-implantation identification of individuals with higher susceptibility to implant-related adverse outcomes, as well as for monitoring patients with metal implants for early detection and therapeutic management of implant-related adverse outcomes.

Contact for Questions and Collaborations

CDRH welcomes the opportunity to interact and/or collaborate with investigators and researchers who are currently engaged in or considering research efforts relate to host response to device implants (regardless of the implant material). Those who are interested may contact us at CDRHResponse@fda.hhs.gov using the title "Implant Research."

[1] FDA supports the principles of the "3Rs," to reduce, refine, and replace animal us in testing when feasible. We encourage sponsors to consult with us if it they wish to use a non-animal testing method they believe is suitable, adequate, qualified for us with medical devices, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

[2] The following references provide examples of the use of in silico approaches for medical applications:

i. In silico approaches for enhancing retrieval analysis as a source for discovery of implant reactivity-related mechanisms and biomarkers. Toroyan Y, Spece H, Goodacre N, Azarbaijani Y, Marinac-Dabic D, Kurtz SM.J Biomed Mater Res B Appl Biomater. 2020 Jan;108(1):263-271. PMID: 31012261

ii. Development of an Integrated Platform Using Multidisciplinary Real-World Dati to Facilitate Biomarker Discovery for Medical Products. Dabic S, Azarbaijani Y, Karapetyan T, Loyo-Berrios N, Simonyan V, Kitchner T, Brilliant M, Toroyan Y. Clin Transl Sci. 2020 Jan;13(1):98-106. PMID: 31386280